Psychosexual Characteristics of Men and Women Exposed Prenatally to Diethylstilbestrol

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Background. Between 1939 and the 1960s, the synthetic estrogen diethylstilbestrol (DES) was given to millions of pregnant women to prevent pregnancy complications and losses. The adverse effects of prenatal exposure on the genitourinary tract in men and the reproductive tract in women are well established, but the possible effects on psychosexual characteristics remain largely unknown.

Methods. We evaluated DES exposure in relation to psychosexual outcomes in a cohort of 2,684 men and 5,686 women with documented exposure status.

Results. In men, DES was unrelated to the likelihood of ever having been married, age at first intercourse, number of sexual partners, and having had a same-sex sexual partner in adulthood. DES-exposed women, compared with the unexposed, were slightly more likely to have ever married (odds ratio [OR] = 1.1; confidence interval [CI] = 1.0–1.4) and less likely to report having had a same-sex sexual partner (OR = 0.7; CI = 0.5–1.0). The DES-exposed women were less likely to have had first sexual intercourse before age 17 (OR = 0.7; CI = 0.6–0.9) or to have had more than one sexual partner (OR = 0.8; CI = 0.7–0.9). There was an excess of left-handedness in DES-exposed men (OR = 1.4; CI = 1.1–1.7) but not in DES-exposed women. DES exposure was unrelated to self-reported history of mental illness in women.

Conclusions. Overall, our findings provide little support for the hypothesis that prenatal exposure to DES influences the psychosexual characteristics of adult men and women.

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Key words: diethylstilbestrol, psychosexual characteristics, sexual behavior, handedness.

From 1939 through the 1960s, the synthetic estrogen diethylstilbestrol (DES) was given to millions of women worldwide to prevent pregnancy complications and losses. In the U.S. alone, as many as 4 million men and women were exposed *in utero* to DES.[1] DES was later shown to be ineffective for its intended purpose,[2] and numerous studies have documented carcinogenic and teratogenic effects on prenatally exposed offspring, including reproductive tract abnormalities in women[3–6]and genitourinary tract abnormalities in men.[4,7,8]

The potential effects of prenatal DES exposure on psychosexual outcomes, however, remain largely unknown. Animal studies suggest that brain organization and hemispheric asymmetry, which affect reproductive behavior and laterality (right *vs* left dominance), are influenced by prenatal hormone exposure.[9–11] To date, most human studies of the influence of DES and psychosexual outcomes have been hampered by small sample sizes and methodological problems. Our large cohort of DES-exposed and unexposed individuals provides a unique opportunity to investigate the influence of prenatal estrogens on psychosexual outcomes, including sexual behavior and laterality (right- *vs* left-handedness) in adult men and women.

Methods

In 1992, the National Cancer Institute (NCI) initiated a combined cohort study of men and women who

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had been exposed *in utero* to DES. The combined cohort included both newly enrolled and previously followed men and women whose DES exposure status was confirmed by either a review of the prenatal medical record or a note from the physician providing prenatal care. The previously followed offspring cohorts were initially assembled in the 1970s and included (1) DES-exposed and unexposed sons and daughters of women who participated between 1951 and 1952 in a randomized clinical trial of DES at the University of Chicago (the Dieckmann cohort); (2) DES-exposed women who, in the late 1970s and 1980s, enrolled in the National Cooperative Diethylstilbestrol Adenosis Project (DESAD cohort), their unexposed sisters and age-matched unexposed women chosen from the same record sources as the exposed; (3) DES-exposed and age-matched unexposed men born between 1939 and 1961 at the Mayo Clinic and (4) DES-exposed men and women, and their unexposed siblings, born between 1943 and 1976 at an infertility clinic in Boston (the Horne cohort). The new cohort consisted of the DES-exposed and unexposed sons and daughters of women who previously participated in the Women's Health Study (WHS); the first follow-up of the offspring cohort occurred in conjunction with the NCI-sponsored combined follow-up in 1994.

The follow-up of the combined offspring cohort has been described previously.[12,13] Briefly, 1% of the potentially eligible women (exposed or unexposed) and 3% of the men (5% exposed, 2% unexposed) had died before the combined study was implemented. An additional 5% of women (5% exposed, 6% unexposed) and 8% of men (7% exposed, 8% unexposed) could not be located, leaving 6,496 women and 3,565 men eligible for participation. Questionnaires were sent by mail. Nonrespondents received a second mailing, after which telephone contact was attempted as needed. We received completed questionnaires from 5,707 of 6,496 (88%) women, representing 3,946 (89%) of the exposed and 1,761 (85%) of the unexposed. Completed questionnaires were also returned by 2,701 of 3,565 (76%) men, representing 1,343 (79%) of the exposed and 1,358 (72%) of the unexposed. The small number of individuals who were less than 21 years of age (21 women, 17 men) were excluded from the analyses. Thus, the analyses were based on 5,686 women and 2,684 men.

The 1994 questionnaire obtained information regarding health events and demographic, reproductive and behavioral factors. In the present analysis, factors of interest for men and women were marital status, sexual behavior and handedness (defined as the hand usually used for writing). Questions regarding sexual behavior included the sex of sexual partners in adulthood, and, for those reporting heterosexual contact, the age at first sexual intercourse and the number of sexual partners. Male participants were asked to report structural genital conditions (undescended testicles, abnormalities of the penis). Women were asked to report a diagnosis and treatment for depression or other mental illness. Reports of specific mental illnesses were coded using ICD-9 classifications and grouped, in consultation with a clinical psychologist, as follows: depression (code 311), anxiety (3000–3009), psychoses (2959–2969) and reactive conditions (3083–3099). Because of small numbers, the eating disorders anorexia (7830), anorexia nervosa (3071) and bulimia (7836) were grouped together for analyses.

The preliminary analyses included descriptive statistics and frequencies. We computed odds ratios (OR) and 95% confidence intervals (CI) using logistic regression models to assess the strength of the association between DES and dichotomous psychosexual outcomes.[14] In general, the OR were adjusted for age, cohort and education. The results of likelihood ratio tests, evaluating homogeneity of the OR across the cohorts for the main factors of interest, supported combining the cohorts for analysis. To assess the possibility that new cohort members had participated in the study because of perceived DES-related health effects, we also evaluated DES in relation to outcomes in the subgroups of newly enrolled and previously enrolled study participants. The associations between DES exposure and outcomes of interest were similar for these two groups; consequently, the analyses reported here are based on all 1994 questionnaire respondents.

Results

The age distribution of DES-exposed and unexposed study participants was roughly comparable, although exposed women tended to be younger than the unexposed (Table 1). Level of education was high overall and higher for the DES exposed than for the unexposed. Study participants were predominantly white.

The distribution of psychosexual characteristics by exposure status is shown in Table 2. A comparable proportion of exposed and unexposed women were left handed, but there was a small excess of left-handedness in the exposed men. Ninety-five percent of men and women reported exclusively heterosexual partners, regardless of exposure. The proportion of study subjects who reported ever having been married was similar for exposed and unexposed women, but slightly lower for the DES-exposed men, compared with the unexposed. Exposed men and women were slightly older at the time of first sexual intercourse compared with their unexposed counterparts. Slightly fewer exposed than unexposed women reported more than one sexual partner.

Table 3 shows the associations between DES and outcomes of interest, adjusted for age, cohort and edu-

TABLE 1. Distribution of Demographic Factors in DES-Exposed and Unexposed Women and Men

	Women		Men	
	DES-Exposed (N = 3,946)	Unexposed (N = 1,740)	DES-Exposed (N = 1,342)	Unexposed (N = 1,342)
	Number (%)	Number (%)	Number (%)	Number (%)
Age				
<35	663 (17)	166 (10)	230 (17)	149 (11)
35–39	1,037 (26)	422 (24)	156 (12)	260 (19)
40–44	1,640 (42)	711 (41)	502 (37)	570 (43)
45+	584 (15)	332 (25)	408 (34)	276 (27)
Cohort*				
Dieckmann	232 (6)	210 (12)	199 (15)	182 (14)
DESAD	3,226 (82)	838 (48)		
Mayo			647 (48)	581 (43)
Horne	213 (5)	125 (7)	247 (18)	144 (11)
WHS	275 (7)	567 (33)	249 (19)	435 (32)
Education				
High school grad or less	543 (14)	358 (21)	229 (17)	276 (21)
Some post–high school	901 (23)	437 (25)	270 (20)	337 (25)
College grad or more	2,493 (63)	940 (54)	832 (63)	727 (54)
Ethnicity				
Nonwhite	72 (2)	45 (3)	30 (2)	21 (2)
White	3,870 (98)	1,689 (97)	1,305 (98)	1,317 (98)

* See text for descriptions of these cohorts.

cation. There was no indication that handedness was influenced by DES exposure in women. DES-exposed men, compared with the unexposed, were more likely to be left handed or ambidextrous than right handed (OR = 1.4; CI = 1.1–1.7). The association was similar after excluding ambidextrous men (OR = 1.3; CI = 1.1–1.7).

In women, DES exposure was not associated with the likelihood of ever having had sexual contact (Table 3). The DES-exposed women, compared with the unexposed, were slightly more likely to have ever married (OR = 1.1; CI = 1.0–1.4). Among the women who reported sexual intercourse with a man, those who were DES exposed were less likely to have had sexual intercourse before age 17 (OR = 0.7; 95% CI = 0.6–0.9) or to have had more than one sexual partner (*vs* 1) (OR = 0.8; CI = 0.7–0.9); in a separate polychotomous regression analysis, similar results were observed for two to nine partners and for ten or more partners (*vs* 1). DES-

TABLE 2. Distribution of Psychosexual Characteristics in DES-Exposed and Unexposed Women and Men

	Women		Men	
	DES-Exposed (N = 3,946)	Unexposed (N = 1,740)	DES-Exposed (N = 1,342)	Unexposed (N = 1,342)
	Number (%)	Number (%)	Number (%)	Number (%)
Handedness				
Right	3,504 (89)	1,558 (89)	1,137 (85)	1,187 (89)
Left	424 (11)	195 (11)	192 (14)	149 (11)
Ambidextrous	13 (<1)	5 (<1)	7 (1)	2 (<1)
Sexual partners				
Only opposite sex	3,655 (95)	1,599 (95)	1,247 (95)	1,257 (95)
Mostly opposite sex	83 (2)	40 (2)	18 (1)	16 (1)
Mostly same sex	30 (1)	16 (1)	9 (1)	9 (1)
Only same sex	16 (<1)	6 (<1)	11 (1)	8 (1)
No sexual contact	57 (2)	21 (1)	25 (2)	28 (2)
Marital status				
Never married	574 (15)	244 (14)	254 (19)	225 (17)
Married	2,796 (72)	1,198 (69)	921 (69)	969 (72)
Widowed	23 (1)	17 (1)	7 (1)	1 (<1)
Divorced/separated	507 (13)	260 (15)	155 (12)	147 (11)
Age 1st intercourse*				
11–16	598 (16)	324 (20)	252 (20)	293 (24)
17–18	1,130 (31)	482 (30)	432 (35)	428 (34)
19–20	993 (27)	423 (26)	284 (23)	278 (22)
21+	979 (27)	389 (24)	267 (22)	249 (20)
Number of partners*				
1	882 (24)	354 (22)	235 (19)	234 (19)
2–9	1904 (51)	885 (54)	559 (45)	552 (44)
≥10	950 (25)	397 (24)	463 (37)	464 (37)

* Among persons who ever had intercourse with an opposite sex partner.

TABLE 3. Association Between DES Exposure and Psychosexual Characteristics, by Sex

Characteristic	Women		Men	
	OR	95% CI	OR	95% CI
Left-handed/ambidextrous	1.0	0.8–1.2	1.4	1.1–1.7
Ever had sexual contact (any)	0.9	0.5–1.5	1.3	0.8–2.4
Ever married	1.1	1.0–1.4	1.0	0.8–1.3
Age 1st intercourse <17†	0.7	0.6–0.9	1.0	0.8–1.2
>1 sexual partner‡	0.8	0.7–0.9	1.1	0.9–1.3
Any same-sex sexual partners‡	0.7	0.5–1.0	1.3	0.8–2.1

* Comparison of DES exposed to unexposed, adjusted for age (4 categories), cohort (4 categories) and education (3 categories).
† Among persons who ever had intercourse with an opposite sex partner.
‡ Among persons who ever had any sexual contact.

exposed women were somewhat less likely, compared with the unexposed, to have had a same-sex sexual partner (OR = 0.7; CI = 0.5–1.0).

In men, the OR for ever having had sexual contact was 1.3 for the exposed (CI = 0.8–2.4) (Table 3). There was no evidence that DES was associated with the likelihood of a man ever having been married. Among men reporting sexual intercourse with a woman, DES was not associated with the total number of sexual partners or with having first intercourse before the age of 17. The OR for more than one partner (*vs* 1) was 1.1 (CI = 0.9–1.3); similar results were observed for two to nine partners and for ten or more partners. The OR for exposed men having had a same-sex sexual partner was 1.3 (CI = 0.8–2.1). We found similar results when the analyses were stratified on the presence or absence of structural genital conditions that might influence sexual behavior.

Sixteen percent of DES-exposed women and 17% of unexposed women reported having been diagnosed and treated for mental illness, and about 10% of these reported more than one condition. Among those reporting any mental illness, 78% reported depression, 15% experienced anxiety, 6% reported both depression and anxiety and 6% reported a psychosis. We found no evidence that women exposed to DES, compared with the unexposed, were more likely to report mental illness overall (OR = 1.0; CI = 0.8–1.1) or to report a diagnosis of depression (OR = 1.0; CI = 0.8–1.2), anxiety (OR = 0.9; CI = 0.6–1.4) or psychosis (OR = 1.2; CI = 0.7–2.2). The results regarding depression were comparable when cases of mild depression or dysthymia were removed from the grouping. We found little evidence that DES exposure was associated with anorexia or bulimia, whether evaluated in all women (OR = 1.1; CI = 0.4–3.1), or in the subgroup of women reporting no other psychiatric condition (6 exposed cases, 2 unexposed; unadjusted OR = 1.3; CI = 0.3–6.5).

Discussion

In animal studies, estradiol (aromatized from testosterone in the fetal brain) plays an important role in masculine sexual differentiation, affecting brain organization and reproductive behavior.[15–16] DES is a potent estrogen and remains biologically active when it reaches target tissues in the developing brain.[10] In addition, the doses of DES given to pregnant women were high; in the U.S., the total dose administered during pregnancy typically ranged from about 1.4 to 11.5 grams,[17] exceeding by 7- to 300-fold the annual dose of DES used for postmenopausal hormone replacement therapy (0.037–0.18 g).[18] Because estrogen can affect fetal brain development, the behavioral and psychological characteristics of adults who were exposed prenatally to DES warrant examination.

The possible influence of prenatal hormones on human psychosexual characteristics, including sexual orientation, is widely hypothesized.[19–21] Several studies have investigated DES in relation to psychosexual outcomes,[22–28] but most enrolled fewer than 80 DES-exposed individuals[22,23,26–28] or had methodological limitations, including use of controls with positive Pap smears[22] or unverified DES exposure status.[24,25] Our study, which was based on more than 5,600 women and 2,600 men, represents the world's largest established cohort of individuals with documented prenatal DES exposure. Thus, the present study offers a unique opportunity to examine questions of longstanding interest.

Our data suggest that DES exposure does not alter a man's likelihood of ever having had sexual contact or having been married. A follow-up report of 46 men whose diabetic mothers participated in a clinical trial of DES indicated that the DES-exposed men in their study were less likely than the unexposed to be married or living as married.[4] Although the authors suggested that DES interfered with sexual function, the overall percent of men who had fathered at least one pregnancy was comparable for the exposed and unexposed groups. Two larger studies, including an analysis of 494 men in the Dieckmann cohort, found no association between DES and ever having been married.[7,24] Our finding that DES was unrelated to the age of first sexual intercourse is consistent with the earlier report based on the Dieckmann men.[7] We found no evidence that DES was associated with a man's number of sexual partners or with the likelihood of sexual contact with other men.

In this study, women exposed to DES *in utero* showed no material change in the likelihood of eventual sexual contact. If anything, our data indicated that the DES-exposed women were slightly more likely to have married than the unexposed. This is similar to findings from a previous study of 315 women whose mothers participated in a DES clinical trial.[24] We found no evidence that exposed women had an increased likelihood of sexual contact with other women.

Our data indicated that the DES-exposed women were older at first sexual intercourse and had fewer

sexual partners in total. These small differences could reflect residual confounding by socioeconomic status, although similar results were not apparent in men, and subcohort analyses did not support this explanation. Exploratory analyses showed that the association between DES and sexually conservative behavior was more apparent in younger women (born after 1955), *ie*, those who reached sexual maturity after the adverse consequences of DES exposure had been reported (early 1970s). Consequently, awareness of the possible adverse effects of DES exposure may have resulted in more sexually conservative behavior. These associations may also have been caused by participation or reporting bias.

A possible influence of prenatal hormones on brain-behavior asymmetries in laboratory animals was suggested by sex differences—present from birth—in the postural laterality of rats (*ie*, tail bias).[9] Laboratory studies have shown that the prenatal administration of androgens can reverse the usual laterality in female rats (although not in males); the shift is attributed to estradiol, aromatized from testosterone in the fetal brain.[9] An analogous shift in handedness, postulated for DES-exposed women,[9,16] has been observed in previous studies.[25–27] However, the results were based on small numbers (fewer than 200 DES-exposed women) and were not adjusted for age, which is strongly associated with left-handedness.[29] Our findings, which were age-adjusted, showed no evidence of an association between DES and handedness in women.

We did note a greater frequency of left-handedness in DES-exposed men, which has not been reported previously. Because medical complications during pregnancy or birth are associated with left-handedness,[30] the relationship noted here among men could reflect a higher rate of pregnancy complications, an indication for DES use, in the exposed mothers. Subgroup analyses showed, however, that the association was strongest (although with a broad CI) in the Dieckmann men, whose mothers were exposed to DES through participation in a clinical trial, thus minimizing the possibility of confounding by indication. Interestingly, mothers participating in the Dieckmann trial received unusually high doses of DES (about 12 g). Our results are consistent with the possibility that DES influences cortical hemispheric organization in the human male fetus, causing a shift in handedness, although this remains speculative.

A few studies have examined the possible association between DES exposure and mental illness,[24,31,32] but only one enrolled more than 50 exposed individuals.[24] The largest of these (264 men, 266 women) found increased depression and anxiety among the DES-exposed sons and daughters of women who had participated in a DES clinical trial; because these conditions were reported by the general practitioner, who was unaware of the patient's DES exposure status, differential reporting bias seems unlikely.[24] Such associations, when observed, might reflect either a biological influence of DES exposure or distress caused by awareness of the possible health effects of DES exposure. We found no association between prenatal DES exposure and reported mental illness in women, although effects may have been attenuated by the use of self-reported data, and those with serious mental illness might not have participated in this study.

It has been suggested that the masculinizing effects of prenatal exposure to DES could result in estrogen-induced nausea and food aversion when the woman reaches sexual maturation. In the extreme case of anorexia or bulimia, estrogen production is reduced, thus palliating the nausea and reinforcing the eating disorder.[33] We found no indication that prenatal DES-exposure was associated with anorexia or bulimia, although a possible association with anorexia was noted in a previous study,[24] and an earlier evaluation of the DESAD cohort found an association with anorexia or bulimia.[33]

Our study has potential limitations. Although the ability to locate and enroll cohort members was good overall, participation was suboptimal for the Dieckmann cohort, introducing the possibility of biased outcomes. However, in analyses stratified by cohort, results for the Dieckmann group were similar to those of the other cohorts. A related issue, affecting all the cohorts, is that willingness to participate may have been influenced by health concerns or pre-existing conditions; in particular, participation may have been higher in exposed persons with DES-related conditions. The outcomes studied here would seem unlikely to influence participation differentially for the exposed and unexposed, and our results were comparable for the previously and newly enrolled participants. Also, we found little evidence, in men, that results differed among those who were affected by urogenital conditions that have been associated with DES exposure. Another potential limitation of our study is the use of sibling controls in some of the cohorts; this introduces the possibility of correlated outcomes in the exposed and unexposed groups. However, findings for the Horne cohort (in which all unexposed participants were siblings of the exposed) were similar to those of the other cohorts.

In summary, our data suggest that prenatal exposure to DES, a potent synthetic estrogen, does not materially influence sexual behavior in adult offspring. In particular, we saw no increase in the likelihood of homosexual contact, a possibility that has been widely hypothesized. We noted a relation between DES exposure and left-handedness in men, a finding that may be consistent with an influence of DES on cortical asymmetry and laterality. Although we found no association between DES exposure and mental illness in women, the question is not easily addressed in these data because survey

respondents may under represent those affected by mental illness and may misclassify outcomes in these self-reported data.

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References

1. Noller KL. In utero exposure to diethylstilbestrol. In: Jones HW III, Wentz AC, Burnett LS, eds. *Novak's Textbook of Gynecology*. 11th ed. Baltimore: Williams and Wilkins, 1988;623–642.
2. Goldstein PA, Sacks HS, Chalmers TC. Hormone administration for the maintenance of pregnancy. In: Chalmers I, Enkin M, eds. *Effective Care in Pregnancy and Childbirth*. Oxford: MJNC Keirse, 1989;612–623.
3. Kaufman RH, Binder GL, Gray PM Jr, Adam E. Upper genital tract changes associated with exposure in utero to diethylstilbestrol. *Am J Obstet Gynecol* 1977;128:51–59.
4. Beral V, Colwell L. Randomised trial of high doses of stilboestrol and ethisterone therapy in pregnancy: long-term follow-up of the children. *J Epidemiol Comm Health* 1981;35:155–160.
5. Herbst AL, Scylly RE. Adenocarcinoma of the vagina. Association of maternal stilboestrol therapy with tumor appearance in young women. *N Engl J Med* 1978;284:878–881.
6. Palmer JR, Hatch EE, Rao S, *et al.* Infertility among women exposed prenatally to diethylstibestrol. *Am J Epidemiol* 2001;154: 316–321.
7. Wilcox AJ, Baird DD, Weinberg CR, Hornsby PP, Herbst AL. Fertility in men exposed prenatally to diethylstilbestrol. *N Engl J Med* 1995;332:1411–1416.
8. Gill WB, Schumacher GFB, Bibbo M, Straus FH, Schoenberg HW. Association of diethylstilbestrol exposure in utero with cryptorchidism, testicular hypoplasia and semen abnormalities. *J Urol* 1979;122:36–39.
9. Denenberg VH. Behavioral asymmetry. In: Geschwind N, Galaburda AM. *Cerebral Dominance. The Biological Foundations*. Cambridge: Harvard University Press, 1984;134–146.
10. Geschwind N, Galaburda AM. Cerebral lateralization. Biological mechanisms, associations, and pathology: II. A hypothesis and a program for research. *Arch Neurol* 1985;42:521–552.
11. Hines M. Prenatal gonadal hormones and sex differences in human behavior. *Psychol Bull* 1982;92:56–80.
12. Hatch EE, Palmer JR, Titus-Ernstoff L, *et al.* Cancer risk after long-term follow-up of women exposed to diethylstilbestrol (DES) in utero. *JAMA* 1998;280:630–634.
13. Strohsnitter WC, Noller KL, Hoover RN, *et al.* Cancer risk in men exposed *in utero* to diethylstilbestrol. *J Natl Cancer Inst* 2001;93: 545–541.
14. Breslow NE, Day NE. *The Design and Analysis of Case-Control Studies*. IARC Scientific Publication No. 32. Lyon, France: International Agency for Research on Cancer, 1980.
15. Gorski RA, Jacobson CD. Sexual differentiation of the brain. *Front Horm Res* 1982;10:1–14.
16. Geschwind N, Galaburda AM. Sex hormone influences on brain growth. In: Geschwind N, Galaburda AM, eds. *Cerebral Lateralization. Biological Mechanisms, Associations, and Pathology*. Cambridge: MIT Press, 1987;105–117.
17. Giusti RM, Iwamoto K, Hatch EE. Diethylstilbestrol revisited: a review of the long-term health effects. *Ann Intern Med* 1995;122: 778–788.
18. Noller KL, Fish CR. Diethylstilbestrol usage: its interesting past, important present, and questionable future. *Med Clin North Am* 1974;58:793–810.
19. Meyer-Bahlburg HFL, Ehrhardt AA, Rosen LR, *et al.* Prenatal estrogens and the development of homosexual orientation. *Dev Psychol* 1995;31:12–21.
20. Anonymous. Sexual behaviour and the sex hormones. *Lancet* July 7, 1979:17–18.
21. Ehrhardt AA, Meyer-Bahlburg HFL, Rosen LR, *et al.* Sexual orientation after prenatal exposure to exogenous estrogen. *Arch Sex Behav* 1985;14:57–75.
22. Meyer-Bahlburg HFL, Ehrhardt AA, Rosen LR, *et al.* Psychosexual milestones in women prenatally exposed to diethylstilbestrol. *Horm Behav* 1984;18:359–366.
23. Yalom ID, Green R, Fisk N. Prenatal exposure to female hormones. *Arch Gen Psychiatry* 1973;28:554–561.
24. Vessey MP, Fairweather DVI, Norman-Smith B, Buckley J. A randomized double-blind controlled trial of the value of stilboestrol therapy in pregnancy: long-term follow-up of mothers and their offspring. *Br J Obstet Gynecol* 1983;90:1007–1017.
25. Scheirs JGM, Vingerhoets AJJM. Handedness and other laterality indices in women prenatally exposed to DES. *J Clin Exp Neuropsychol* 1995;17:725–730.
26. Smith LL, Hines M. Language lateralization and handedness in women prenatally exposed to diethylstilbestrol (DES). *Psychoendocrin* 2000;25:497–512.
27. Schacter S. Handedness in women with intrauterine exposure to diethylstilbestrol. *Neuropsychologia* 1994;32:619–623.
28. Reinisch JM, Sanders SA. Effects of prenatal exposure to diethylstilbestrol (DES) on hemispheric laterality and spatial ability in human males. *Horm Behav* 1992;26:62–75.
29. Titus-Ernstoff L, Newcomb PA, Egan KM, *et al.* Left-handedness in relation to breast cancer risk in postmenopausal women. *Epidemiology* 2000;11:181–184.
30. Bakan P, Dibb G, Reed P. Handedness and birth stress. *Neuropsychol* 1973;11:363–366.
31. Fried-Cassorla M, Scholl TO, Borow LD, Strassman HD, Bowers EJ. Depression and diethylstilbestrol exposure in women. *J Reprod Med* 1987;32:847–850.
32. Pillard RC, Rosen LR, Meyer-Bahlburg H, *et al.* Psychopathology and social functioning in men prenatally exposed to diethylstilbestrol (DES). *Psychosom Med* 1993;55:485–491.
33. Gustavson CR, Gustavson JC, Noller KL, *et al.* Increased risk of profound weight loss among women exposed to diethylstilbestrol in utero. *Behav Neural Biol* 1991;55:307–312.